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INSIDE

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Daptomycin: Safe at Higher Doses?

ABSTRACT & COMMENTARY

By Brian Blackburn, MD

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Dr. Blackburn reports no financial relationships relevant to this field of study.

Source: Figueroa DA, et al. Safety of High-Dose Intravenous Daptomycin Treatment: Three-Year Cumulative Experience in a Clinical Program. *Clin Infect Dis*. 2009;49:177-180.

Synopsis: *A retrospective review of 61 patients treated with high-dose daptomycin (mean dose, 8 mg/kg/day) for various indications resulted in few major side effects; three patients experienced symptomatic CPK elevations necessitating drug discontinuation. Although these data are preliminary, high-dose daptomycin may be a safe alternative in patients with serious gram-positive infections.*

DAPTOMYCIN IS A LIPOPEPTIDE ANTIBIOTIC THAT EXHIBITS CONcentration-dependent bactericidal activity against a wide array of gram-positive organisms. It is approved for the treatment of complicated skin and soft-tissue infections (SSTI) at a dose of 4 mg/kg/day, as well as for *Staphylococcus aureus* bloodstream infections at a dose of 6 mg/kg/day. At these doses, clinical trials have shown daptomycin to be non-inferior to comparator drugs, but demonstration of superiority has remained elusive; in addition, "MIC creep," while on therapy, has been observed in over 5% of patients in some trials.[1] The drug's concentration-dependent killing makes it a tempting target for attempts at the use of increased doses, and in-vitro data suggest that higher doses can lead to more potent activity.[2] In addition, endocarditis caused by highly resistant bacteria such as methicillin-resistant *S. aureus* (MRSA) or vancomycin-resistant *Enterococcus* (VRE), can be difficult to effectively treat, leading some clinicians to attempt higher doses. Figueroa et al, therefore, undertook a retrospective study to assess the safety of increased doses of this drug in clinical practice.

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All patients who had received daptomycin from 2004-2007 at a single center in New York City were identified retrospectively through an electronic database; patients were then included in the study if they had received a dose above 6 mg/kg/day for two or more weeks. While on daptomycin, all patients had all concomitant 3-hydroxy-3-methylglutaryl-coenzyme A (HMG CoA)-reductase inhibitors held. Daptomycin was dosed every 24 hours unless a patient's creatinine clearance was < 30 mL/min, in which case, it was dosed every 48 hours; dosing was based on actual body weight.

Sixty-one patients were included in the cohort, with a median age of 67 years. Infections by site included 43% with bloodstream infections, 23% with SSTIs, 15% with bone/joint infections, 10% with left-sided endocarditis, and 8% with intra-abdominal infections. Infecting organisms included methicillin-resistant *S. aureus* (26% of patients), methicillin-susceptible *S. aureus* (3%), methicillin-resistant *Staphylococcus epidermidis* (5%), *Enterococcus faecium* (15%), and *Enterococcus faecalis* (15%).

Patients received a mean dose of 8 mg/kg/day of daptomycin, for a median of 25 days (range 14-82 days). Baseline and follow-up laboratory testing of creatine phosphokinase (CPK) was not done systematically; three patients had no testing done and, of the remaining 58, most had some CPK testing done during therapy, though testing was often erratic and precise figures were not given.

Twenty-two (36%) patients experienced at least one mild adverse event (such as anemia, diarrhea, nausea, hypokalemia, or arthralgias). Three (5%) experienced CPK elevations above 1,000 U/L, with concomitant constitutional and/or musculoskeletal complaints. Daptomycin was stopped in all three with resolution of these abnormalities. Two of these three patients were obese (BMI "grade III").

■ COMMENTARY

Daptomycin at a mean dose of 8 mg/kg/day was well tolerated in this cohort, one of the largest series of patients treated with high-dose daptomycin to date. Although historical safety data involving daptomycin at these doses are relatively limited, the use of high-dose daptomycin is not without precedent. A small cohort of healthy volunteers tolerated doses up to 12 mg/kg/day4 without any evidence of muscle toxicity. Other small clinical series and case reports have documented doses up to 10-12 mg/kg/day, most with minimal adverse effects.[5-8] Although just under 5% experienced significant and symptomatic CPK elevations in the current study, this is only slightly higher than that seen in a key clinical trial involving standard-dose daptomycin.[1] While this does mandate close CPK monitoring, it also suggests that with appropriate supervision, this adverse effect can be managed, and that this dose may not be significantly more toxic than standard-dose daptomycin.

Although efficacy data are not presented, this study represents an encouraging finding, as it paves the way for future studies to examine efficacy. It is particularly important given the rising MICs seen on standard-dose daptomycin therapy in a recent trial;[1] perhaps the use of higher doses will mitigate this problem. In addition, although not licensed for this indication, daptomycin is frequently used for systemic enterococcal infections. Given that enterococci typically have higher MICs to daptomycin than *S. aureus* or other gram-positive organisms,[3] it will be interesting to see if the use of higher doses makes a clinical difference in trials involving these organisms.

A particularly encouraging aspect of this study is the length of daptomycin therapy employed; all subjects received the drug for at least two weeks, and the median length of therapy was nearly four weeks. This may indicate that the use of high-dose daptomycin is safe, even for indications that require prolonged use, such as endocarditis and bone/joint infections. This will be a key aspect to monitor in future studies.

An intriguing finding of this study is that two of the three patients who experienced severe CPK elevations were obese; perhaps difficulty in accurately estimating

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Questions & Comments

Leslie Hamlin,
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dosing based on creatinine clearance and use of actual body weight in these cases led to inappropriately high dosing in these patients. This is another issue that should be examined closely in future studies. It is important to note that all patients in this study had concomitant HMG CoA-reductase therapy held during daptomycin treatment. Whether this is routinely necessary in patients treated with high-dose daptomycin is not clear, but the results from this paper may only be applicable in such a circumstance.

The limitations of this paper include the relatively small cohort and retrospective nature of the study. Several inherent biases result, such as the possibility of underreporting of adverse events, particularly given that not all patients in this cohort had CPK testing done at regular intervals. Nevertheless, these preliminary data are encouraging, and herald the next step of assessing the efficacy of high-dose daptomycin, as well as a careful assessment of adverse effects in a randomized, blinded trial. ■

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Multiple Test Methods for the Detection of Novel H1N1

ABSTRACT & COMMENTARY

By Ellen Jo Baron, PhD, D(ABMM)

Professor of Pathology, Associate Director, Clinical Microbiology Laboratory, Interim Director, Clinical Virology Laboratory, Stanford University Medical Center

Dr. Baron reports no financial relationships relevant to this field of study.

Synopsis: *At least two current commercially available and widely used rapid antigen tests performed poorly on respiratory samples with low sensitivity for detecting both the regularly circulating influenza A and B strains this season, but they also failed to detect the novel influenza A H1N1 (swine-origin) influenza in the majority of specimens tested. The sensitivity of direct fluorescent antibody stain assays seems to vary among laboratories. A new multiplex bead based assay (Luminex technology) was the best performing among all test methods.*

Source: Ginocchio CG, et al. Evaluation of multiple test methods for the detection of the novel 2009 influenza A (H1N1) during the New York City outbreak. *J Clin Virology*. 2009;45:191-195.

THE ENERGETIC CHRISTINE GINOCCHIO (DIRECTOR OF Clinical and Molecular Microbiology Laboratories for North Shore-Long Island Jewish Healthcare System) began receiving an unusual gift beginning on April 24, 2009. A group of local New York schoolboys had just returned from Cancun, Mexico, with influenza-like illness rampant among them, which spread quickly throughout the community. News was hitting the airwaves about a new "swine flu" outbreak in Mexico. Dr. Ginocchio's laboratory received more than 6,000 respiratory samples to test within five weeks. She was able to use this treasure trove of patient material to run assays using several methods to determine how the methods compared for detection of the novel virus. Almost

before June began, and in plenty of time for other laboratories to benefit from the New York experience, the study had been written up and published. The speed of this accomplishment mirrors that of the local administration's response to her plea for more laboratory capacity. In a special session at the American Society for Microbiology General Meeting in Philadelphia, called to discuss the novel H1N1 influenza, Dr. Ginocchio told the stunned audience that her facility was able to convert two administrative rooms into a functioning virology laboratory complete with two biosafety level 2 cabinets over one weekend — surely a record for creating a laboratory from scratch, and a tribute to the dedication and leadership of her administration. Many other administrators, laboratory scientists, and laboratory industry employees all over the United States (and Mexico) spent numerous sleepless nights and long, tiring days responding to the explosive spread of this new influenza. The laboratory at Stanford, for example, after already having discontinued use of rapid antigen tests due to both poor sensitivity and poor specificity, started processing direct fluorescent antibody tests around the clock in response to demand, going from a high of 50 the week before April 24th to 250 samples during the first week of the outbreak in our local area. These numbers, however, pale in comparison with those submitted to the North Shore-Long Island Jewish microbiology/virology laboratory.

The Luminex platform utilizes tiny beads to which either antigens, antibodies, or oligonucleotides that bind a bit of DNA can be attached. The beads come in 100 subtly different fluorescent colors so that it would be possible to create a multiplex assay that could detect up to 100 different analytes in one suspension. When the ligand of interest has bound to the beads, the beads are fed in a stream similar to that of a cell-sorting device where laser lights can interrogate the bead's fluorescence to determine the specific ligand, as well as how many beads actually have bound their targets. The results are a semi-quantitative determination of what targets were in the sample. The Luminex Diagnostics Company in Toronto, Canada, has developed a multiplex assay for respiratory viruses, called xTAG Respiratory Virus Panel (RVP). A total of 12 different respiratory viruses are detected in the system, which requires sample extraction (usually on the NucliSens EasyMag system, available from bioMerieux), amplification by PCR of multiple virus targets, attachment of the amplified targets to specific beads with matching sequences, and reading the information from the beads in a flow-cytometer-like reader instrument. Turnaround time is usually around 24 hours due to the multiple steps required and the need to batch samples for testing. A previous publication on the Luminex platform[1] showed that the system was 10- to 100-fold less sensitive than individual real-time PCR tests for each virus individually but that, in their study of previously positive clinical samples, there were virtually no false-negative results. With a small number of prospective samples (18), Ginocchio et al were surprised to find 22% of samples had two viruses detected by the PCR method, whereas cultures and DFA methods usually report only one virus.

■ COMMENTARY

Ginocchio et al performed more than 2,700 xTAG RVP tests in comparison with rapid antigen (two different manufacturers), DFA, and culture. The largest percentage (40.8%) of the samples were positive for the variant swine-origin H1N1. The next closest prevalent virus was rhinovirus, at 16.6%. Once the new H1N1 enters the population, the other influenza A viruses are quickly supplanted. This also is being seen at our own facility, where around 99% of influenza A detected are the new flu. One would suspect that viruses seen now in the New York area also will be primarily the novel H1N1, but this study was conducted during the initial stages when other viruses were still circulating. As most laboratories have quickly learned, the rapid antigen tests perform poorly with this influenza A. Before this year, we probably did not realize how insensitive the rapid antigen tests were for the other influenza A strains. The sensitivity of the rapid antigen tests for detecting novel variant H1N1 (adding results from both rapid test kits) was only 23.8%. This is not a test that any physician should continue to request.

In Ginocchio's laboratory, the DFA performed marginally better, with a sensitivity of 50%. This is quite different from the Stanford laboratory's results, at least for respiratory viruses overall. A publication done by one of our pediatric infectious diseases fellows in 2003 compared DFA with culture,[2] and found the sensitivity of DFA (not limited to influenza A) to be 84% in children in whom the test may have greater sensitivity than in adults. That was before we also tested for metapneumovirus by DFA. A more recent publication from the Stanford Virology laboratory[3] comparing DFA to another multiplex molecular respiratory panel (NanoChip400 from Nanogen, since withdrawn from the market) showed the sensitivity of DFA (for influenza A, influenza B, respiratory syncytial virus, and parainfluenzas 1, 2, and 3) to be 94%. Of 122 positive samples tested, the DFA only missed one influenza A (the age of the subjects was not stated). This study was conducted before the novel H1N1 variant had surfaced. However, anecdo-

tally, this season, whenever cultures or PCR tests (performed at the Santa Clara County laboratory) were compared with the DFA, there have been only rare discrepancies as well. The take-home message about DFA testing for respiratory viruses is that the experience of the clinical laboratory scientists, their care in specimen handling and testing, and the procedures used can lead to large differences in comparability or reliability of results. The DFA test is very dependent on technical expertise and, thus, laboratory performance can vary.

Fortunately, in the near future, many laboratories will have multiplex molecular respiratory virus panel tests that will yield reliable results, as did the RVP in the New York study. On a subset of 288 samples tested by all four methods, the RVP had a sensitivity of 97.8% for detection of novel H1N1 swine-origin influenza, with a positive predictive value of 100% and negative predictive value of 97.3%.[1] The viral culture sensitivity was 88.9%. Although clinicians will suffer a longer wait for the results of the RVP than for either rapid antigen or DFA results, they will be likely to get the best answer. Depending on the quality of their local laboratory, DFA testing, especially given a more rapid time to results, even if testing is batched and performed twice a day, may be a second option.

Mahoney et al have just published a cost analysis of xTAG RVP vs. DFA alone and vs. DFA and rapid culture method (shell vial) to determine the best strategy for testing samples from children in their four Canadian hospitals when the next influenza season hits.[4] The cost analysis included all hospitalization, antibiotic, laboratory testing, and isolation costs. Surprisingly, the costs per case were quite similar regardless of which testing strategy was used, ranging from 903,619 to $3,623. They found that the most cost-effective plan would be to use the RVP alone when the prevalence of infection was 11% and DFA alone when the prevalence was < 11%. If the RVP alone was employed to replace their current protocol of DFA followed by shell vial culture, which requires 48 hours for final results, Mahoney et al estimated that the four hospitals would save more than $500,000 in one year.4 Their turnaround time for DFA alone (only performing at 72% sensitivity in their system) was four hours, and the xTAG RVP turnaround time would be 24 hours. In fact, if they were able to enhance the sensitivity of the DFA in their analysis model, then the outcomes would have slightly favored the DFA test. And since most of the cost savings found with the RVP-alone strategy resulted from decreased hospital length of stay, based on 24-hour results in comparison with their current protocol, which required 48 hours for the culture results, the use of a highly reliable DFA would result in even greater savings.

There are other benefits to multiplex PCR tests, however. As the number of laboratory technical experts in conventional virology dwindle (already beginning to happen), the skills required to perform DFA will also disappear. Automated testing platforms offer the same or better accuracy with less subjectivity. The platforms can also detect more virus types than DFA panels, and certain respiratory viruses, such as adenovirus and rhinoviruses, which are notoriously difficult to detect in either DFA or culture, depending on the virus, can be effectively targeted in molecular assays. And, in a very short time, the automation will increase and the turnaround time will decrease. Perhaps within a year or two, manual virology testing for respiratory viruses will be another technology of the past. ■

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Treatment of Kawasaki Disease

ABSTRACT & COMMENTARY

By Hal B. Jenson, MD, FAAP

Professor of Pediatrics, Tufts University School of Medicine, and Chief Academic Officer, Baystate Medical Center, Springfield, MA

Dr. Jenson is a speaker for Merck.

Synopsis: *During 2001-2006, approximately 15% of children with Kawasaki disease in the United States required re-treatment, and 7% required readmission*

within six weeks. The use of infliximab for immunoglobulin-resistant Kawasaki disease has increased and was 2.3% in 2006.

Source: Son MBF, et al: Treatment of Kawasaki disease: Analysis of 27 US pediatric hospitals from 2001 to 2006. *Pediatrics*. 2009;124:1-8.

A STUDY OF IMMUNOGLOBULIN-RESISTANT KAWASAKI disease in the United States was conducted using data from the Pediatric Health Information System. All patients diagnosed and treated for Kawasaki disease, including readmissions, were identified during 2001 to 2006 among 27 hospitals representing all geographic regions of the country.

During the study period, 4,811 patients with Kawasaki disease had 5,197 admissions. The annual incidence of Kawasaki disease increased 32.6% from 2001 (n = 678) to 2006 (n = 899). Male patients represented 60.4% of all patients. Asian patients were over-represented ($p < 0.001$), constituting 6.9% of patients admitted with a diagnosis of Kawasaki disease, compared with constituting 1.6% of all patients in the database. The median length of stay was three days, and did not change during the six-year study. A total of 351 patients (7.3%) required readmission within six weeks, and 31 patients (8.8% of patients who required re-admission and 0.6% of all patients) required two or more readmissions. Age < 1 year was associated with a greater likelihood of readmission (9.6% vs. 68%, $p = 0.005$). Readmission was not associated with gender, ethnicity, insurance type, or median length of stay of first admission.

Retreatment with intravenous immunoglobulin (IVIG) was administered to 14.8% of patients (n = 712), including 531 patients (11.0%) during their first admission and 213 (60.7%) of the 351 patients who were readmitted (32 patients were retreated with IVIG during both initial and subsequent admissions). Other anti-inflammatory therapies used for immunoglobulin-resistant Kawasaki disease included methylprednisolone (5.8%), orally administered prednisone (2.8%), and infliximab (1%). The proportions of children who received IVIG retreatment and corticosteroids remained stable during this period, and the use of infliximab increased from 0% in 2001 to 2.3% (21 of 899 patients) in 2006.

Antithrombotic therapy included aspirin in 4,429 patients (92%), warfarin in 54 patients (1.1%), enoxaparin in 49 patients (1.0%), tissue plasminogen activator in 33 patients (0.7%), clopidogrel in 16 patients (0.3%), and abciximab in 10 patients (0.2%). Unfractionated heparin was administered to 2,004 patients (41.7%), but its use for maintenance of intravenous access could not be distinguished from its use for therapeutic anticoagulation.

Coronary artery aneurysms were diagnosed in 127 patients (2.6%) during the first admission and in 157 patients (3.3%) overall. Risk factors for coronary artery aneurysms included male gender (3.8% vs. 2.4%, $p = 0.006$), age < 1 year (8.0% vs. 2.2%, $p < 0.001$), and Hispanic ethnicity ($p < 0.001$).

Six patients died during hospitalization, for a mortality rate of 0.12%. The ages ranged from five months to 11 years (median: 29 months); each of the six patients received one or more doses of IVIG and aspirin.

■ COMMENTARY

This is the first large, multicenter report of the current treatment regimens used for Kawasaki disease in the United States. Approximately 15% of patients admitted with Kawasaki disease receive retreatment during initial or subsequent admissions.

In 2004, the American Heart Association and the American Academy of Pediatrics published recommendations for the diagnosis and treatment of Kawasaki disease (*Pediatrics*. 2004;114:1708-1733). IVIG (2 g/kg) and aspirin are the mainstays of initial treatment. Failure to respond is defined as persistent or recrudescent fever ≥ 36 (48) hours after completion of the initial IVIG infusion. For refractory cases, most experts recommend IVIG retreatment with a second dose of IVIG (2 g/kg). There is currently some variability in the agents used for subsequent treatment of immunoglobulin-resistant Kawasaki disease.

Elevated levels of tumor necrosis factor (TNF-α) have been reported in patients with Kawasaki disease, especially those with coronary artery abnormalities and, therefore, the use of infliximab is reasonable, especially for refractory cases. The use of infliximab (Remicade) for Kawasaki disease increased from 0% in 2001 to 2.3% in 2006. Infliximab is a chimeric monoclonal antibody that binds TNF-α and blocks attachment to TNF-α receptors on T cells, which reduces inflammatory response. When used, it is generally administered only once or, at most, twice to children with immunoglobulin-resistant Kawasaki disease. There are no controlled, prospective, clinical trials with adequate power to assess the efficacy and safety of infliximab in the management of Kawasaki disease. A multicenter trial of the safety and efficacy of infliximab vs. a second dose of IVIG for refractory Kawasaki disease is underway. ■

Table

Comparison of Trial-level Meta-analysis of Mortality in Cefepime Trials

	Yahav et al	Not included in Yahav et al	Combined (Yahav et al + others)
# of trials	38	50	88
Risk of all-cause mortality: cefepime vs. comparator at 30 days post-therapy	RR = 1.26 (95% CI, 1.08 to 1.49).Adjusted risk difference = 17.02 per 1,000 population (95% CI, 5.54 to 28.5)	Adjusted risk difference = 2.83 per 1,000 population (95% CI, -11.47 to 5.80)	Adjusted risk difference = 5.83 per 1,000 population (95% CI, -1.53 to 12.28

Cefepime: Out of the Doghouse

SPECIAL COMMENTARY

By Stan Deresinski, MD, FACP

In response to a published metanalysis that concluded that cefepime use was associated with excess mortality,[1] on November 14, 2007, the FDA published an "Early Communication About an Ongoing Safety Review of Cefepime (marketed as Maxipime)."[2] While not confirming the results of that metanalysis, it indicated it was reviewing the subject, and estimated that it would reach a conclusion in approximately four months. Well after four months had elapsed, it issued a statement indicating it was having difficulty accessing all the relevant information. The FDA has now, 19 months after its original missive, published a statement that, for all practical purposes, exonerates cefepime.[3]

The FDA performed meta-analyses using data in addition to the 38 clinical trials examined by Yahav et al,[1] in which patients were subjected to only a trial-level meta-analysis. The FDA, in contrast, performed meta-analyses using both trial-level and patient-level data, and found no statistically significant differences in mortality in patients given cefepime relative to those given comparator antibiotics (*see Table)*. A subset analysis of trials involving patients with febrile neutropenia also showed no statistically significant difference in mortality (adjusted risk difference = 9.67 per 1,000 population [95% CI, -2.87 to 22.21]).

The methodology of Yahav et al was recently examined with the conclusion of their finding that increased mortality associated with cefepime use was unreliable.[4] Yahav et al, however, caution that administration of this antibiotic may be associated with an increased risk of encephalopathy. Encephalopathy has previously been reported with cefepime, as it has with other β-lactam antibiotics, and it frequency may be greatest in patients with renal insufficiency. Thus, Garces et al found that 5 of 498 cefepime recipients developed encephalopathy, which was associated with reduced renal function.[5] This suggests that this complication is concentration- and dose-dependent. ■

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IXIARO®: A New Japanese Encephalitis Vaccine

SPECIAL COMMENTARY

By Stan Deresinski, MD, FACP

Japanese encephalitis virus (JEV), a flavivirus, is transmitted by rice field-breeding mosquitoes who have fed on wild birds, the natural hosts, and domestic pigs, which serve as amplifying hosts.[1] Japanese encephalitis due to JEV is estimated to be the cause of 10,000-15,000 deaths in Asia annually, with significant residual neurological deficits in

approximately one-third of survivors. Countries that have had major epidemics in the past, but that have controlled the disease primarily by vaccination include China, Korea, Japan, Taiwan, and Thailand. Other countries that still have periodic epidemics include Vietnam, Cambodia, Myanmar, India, Nepal, and Malaysia.[2] Travelers visiting endemic areas may be at risk, depending on the season, proximity to rural areas, and outdoor activities pursued. In the United States, an inactivated mouse brain-derived vaccine, JE-VAX®, has been available, but its use was limited, in large part because of associated adverse events, including urticaria, angioedema, and respiratory distress, which often occurred as late as two weeks after vaccination. JE-VAX® is no longer an option since it was recently discontinued and the availability of remaining stocks is severely limited and diminishing. The estimated remaining 4,500 doses of JE-VAX® is being reserved by Sanofi Pasteur for use in younger children. Fortunately, we now have an alternative, at least for adults.

A new inactivated vaccine, IXIARO®, has been demonstrated to have immunogenicity similar to JE-VAX®, with a similar overall safety profile and with somewhat improved tolerability at the site of injection. It is adjuvanted with aluminum hydroxide and contains no gelatin or animal proteins (or thimerosal). Grown in Vero cells, administration of this vaccine in clinical trials resulted in protective antibody titers 56 days after vaccination in 99% of subjects with two doses.[3] After six months, 95% still had protective levels, but this proportion diminished to 83% after one year.[4] In 24 subjects 65 years of age or older, the seroconversion rate was 95.8%. The duration of protection is unknown.

IXIARO® was approved by the FDA on March 30, 2009, for use in individuals 17 years of age and older. The CDC Advisory Committee on Immunization Practices (ACIP) has updated previous recommendations and, importantly, expanded its use to short-term travelers going to non-urban areas with significant outdoor exposure during the transmission season. These do not, however, become official CDC recommendations until they are published in *MMWR*, and this has not yet occurred. Nonetheless, the ACIP recommendations included the following:

• Travelers to countries where the virus is endemic should be advised of the risks of Japanese encephalitis and the importance of measures to reduce mosquito bites.

• Vaccination is recommended for travelers who plan to spend a month or longer in endemic areas during transmission season.[2]

• Vaccination should be considered for short-term travelers to endemic areas during transmission season[2] if they will travel outside of an urban area and their activities will increase the risk of exposure to the virus.

• Vaccination is not recommended for short-term travelers whose visit will be restricted to urban areas or times outside the transmission season.

• Vaccination with regular follow-up to ensure protection is recommended for laboratory personnel who work with live, wild-type strains of the virus.

IXIARO®, which must stored at 2°-8° C, is administered as two intramuscular doses 28 days apart; the second dose should be received at least one week prior to potential exposure to JEV. Coadministration of hepatitis A vaccine does not affect the immunogenicity of IXIARO®. The most frequently encountered adverse events of vaccination, occurring in > 10% of recipients, are headache, myalgia, and injection site pain and tenderness. While appearing safe in clinical trials, caution must be exerted, since the vaccine was tested in fewer than 5,000 subjects, and unexpected adverse reactions may emerge with wider experience.

Those most susceptible to severe manifestations of JEV infection include children < 10 years of age, and IXIARO® has not been approved by the FDA for individuals < 17 years of age. In child travelers who will be at significant risk of JEV infection, it may be possible to access the remaining doses of JE-VAX® until they are depleted or they become outdated in the spring of 2011. Aggressive measures to prevent mosquito exposure, important for all travelers, will assume greater importance in children . ■

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Coartem® for Malaria in the United States

SPECIAL COMMENTARY

By Stan Deresinski, MD, FACP

On April 8, 2009, the FDA approved the use of Coartem® tablets in the treatment of acute, uncomplicated malaria in adults and in children weighing at least 5 kg. Coartem® tablets contain 20 mg artemether and 120 mg lumefantrine, each of which is a blood schizonticide but with dissimilar modes of action.[1] Current evidence indicates that the activity of the artemisinins (of which artemether is one) may result from free radical injury, while that of lumefantrine is undefined, but has been suggested to result from complexation with hemin.

The peak plasma concentrations of artemether and its active metabolite, dihydroartemisinin, are reached approximately two hours after ingestion of Coartem® in tablet form, while that of lumefantrine is not achieved until 6-8 hours. In healthy volunteers, when compared to fasted conditions, ingestion after a high-fat meal increased the absorption and bioavailability of artemether more than two-fold, while that of lumefantrine increased 16-fold. In malaria patients, however, lumefantrine exposure was only increased approximately two-fold when taken after a meal.

Both drugs are primarily metabolized to their active metabolites, dihydroartemisinin and desbutyl-lumefantrine, by hepatic CYP3A4. Artemether does not appear to be a significant inhibitor of CYP45 enzymes at clinically relevant concentration, while lumefantrine may inhibit CYP2D6 and, as a consequence, Coartem® should not be administered with drugs such as some neuroleptics and tricyclic antidepressants, which are metabolized by this isoenzyme. While coadministration of potent inhibitors of CYP3A4, such as ketoconazole, results in increased exposure to the antimalarial, the increase is insufficient to warrant a dose adjustment. Artemether is removed from plasma with a half-life of 2-3 hours, while the T1/2 of lumefantrine is 3-6 days. Although not studied in humans, renal excretion was not detected in animal models.

Studies in a number of geographic venues indicate that Coartem® therapy produces high rates of success in the treatment of infection due to *Plasmodium falciparum*. While less data are available, it is also active in the treatment of *P. vivax* infection (although, as with other therapies, administration of primaquine is required to prevent relapse). In the United States, the only other fixed-dose combination oral therapeutic for *P. falciparum* infection is Malarone®, which is comprised of atovaquone and proguanil. In a randomized trial involving 97 patients with falciparum malaria in southwestern Ethiopia, there were no treatment failures in Coartem® recipients at 28 days, but PCR-confirmed recrudescence rates were 9% in Malarone® and 6% in those treated with quinine.[2] A single recrudescence occurred in a quinine recipient at day 40 and in a Coartem® recipient at day 70. Thus, it seems likely that Coartem® is superior to both Malarone® and quinine.

The recommended Coartem® treatment course consists of a total of six doses over three days. In patients 16 years of age or greater, weighing at least 35 kg, a total of 24 tablets are given: four tablets should be given initially, followed by another four tablets in eight hours later, followed by four tablets twice daily for the following two days. ■

References:

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CME Questions

4. **Which is correct with regard to daptomycin?**
   a. It exhibits time-dependent bacterial killing.
   b. It is active against most Gram negative bacteria.
   c. It causes elevation in creatine kinase in more than 50% of patients given a mean dose of 8 mg/kg daily.
   d. It exhibits concentration-dependent killing.

5. **Which is the least sensitive method of testing for influenza virus in respiratory specimens.**
   a. Direct fluorescent antibody (DFA) testing.
   b. Isolation in cell culture.
   c. Multiplex Respiratory Virus Panel (RVP).
   d. Rapid antigen screening testing.

6. **Which of the following is correct with regard to Coartem?**
   a. It consists of a combination of atovaquone and proguanil.
   b. Its components are prodrugs that are metabolized to active metabolites.
   c. It must be given intravenously.
   d. It is only effective in the treatment of *Plasmodium vivax* infection.

Answers: 4. (a); 5. (d); 6. (b)

CME Objectives

The objectives of *Infectious Disease Alert* are to:

• discuss the diagnosis and treatment of infectious diseases;

• present current data regarding the use of new antibiotics for commonly diagnosed diseases and new uses for traditional drugs;

• present the latest information regarding the pros, cons, and cost effectiveness of new and traditional diagnostic tests; and

• discuss new information regarding how infectious diseases (eg, AIDS) are transmitted and how such information can lead to the development of new therapy. ■

In Future Issues:

Herpes Zoster in Children and Adolescents in the Era of Varicella Vaccination

UPDATES

By Carol A. Kemper, MD, FACP

PANDAS: Rare or Simply Non-existent?

Source: Shulman ST. Pediatric autoimmune neuropsychiatric disorders associated with streptococci (PANDAS): Update. *Current Op Peds*. 2009;21:127-130.

A RECENT CASE OF A 17-YEAR-OLD presenting with acute psychiatric symptoms and possible meningoencephalitis prompted examination of this review article on Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infection (PANDAS). The patient presented with acute-onset fever, mental status changes, and mild CSF pleocytosis (18 cells/mL), with otherwise normal CSF parameters. Evaluation, including radiographic studies and EEG, failed to identify an infectious etiology or other cause. While his mental status continued to wax and wane, he promptly defervesced, and a repeat CSF analysis four days later was unremarkable. Only an ASO titer was elevated at 748. The patient had no arthritis or carditis and no evidence of OCD or tic disorder, although his behavior was often bizarre, with facial grimaces.

Dr. Shulman nicely summarizes the current literature regarding the relationship between a group of neuropsychiatric disorders occurring in children ages 3 to puberty, including Sydenham's chorea, OCD and tic disorder (or Tourette's syndrome), and antecedent group A streptococcal (GAS) infection. The association between Sydenham's chorea and GAS is strongly supported by the literature, mostly because it occurs in patients with arthritis and/or carditis consistent with acute rheumatic fever. Recognition of this type of chorea may be complicated by symptom onset up to six months following GAS infection, when the ASO titer is often negative.

However, a cohort study found no association between OCD/tic disorder and GAS infection in 85% of cases. And no good evidence exists to support differences brain autoimmunity between patients with OCD/tic disorders and those without. Additional studies suggest that PANDAS, most of which do not fit the classical description of OCD/tic disorder, are overdiagnosed by community physicians.

Dr. Shulman concludes that the association between these neuropsychiatric disorders and GAS seems increasingly unlikely. Therefore, long-term antibacterial prophylaxis is not warranted, and there is no clinical evidence to support the use of plasma exchange or IVIG in these children.

In the end, it was revealed that our patient had a history of bipolar disorder, as well as recent ecstasy use, which provided a likelier explanation for his fever and bizarre behavior.

Isolation Precautions for Respiratory MRSA

Source: Gehanno JF, et al. Aerial dispersal of meticillin-resistant *Staphylococcus aureus* in hospital rooms by infected or colonised patients. *J Hosp Infect*. 2009;71:256-262.

INFECTION CONTROL POLICIES VARY regarding the use of face masks in patients with MRSA nasal or respiratory colonization or infection. To assess the potential for airspace contamination in such patients, duplicate air samples were collected within 0.5, 1, and 2-3 meters from the head of patients with MRSA respiratory tract infection (n = 20) or respiratory colonization (n = 4). Sixteen of the patients had received no antibiotics specific for MRSA before the sampling period. Control samples collected were obtained from three rooms before patients were admitted to the space.

Airspace samples were positive for 87.5% of the case patients; in contrast, airspace samples from the control rooms were all negative. Nearly half (49%) of 138 air samples were positive for MRSA, with a range of 1-78 cfu/culture plate (mean, ~7 cfu/plate). The distance from the head of the patient was not significant.

PFGE was used to examine 12 selected pairs of clinical and environmental isolates, demonstrating good concordance. Two major susceptibility profiles were observed among the clinical and environmental isolates, similar to strains circulating in the hospital during the study period. Environmental strains isolated from 13 of 21 rooms had a similar susceptibility profile, and the environmental and clinical isolates appeared to match. Isolates from the other eight rooms differed, with up to three different strains per room, and the clinical and environmental isolates did not appear to match.

These data suggest that MRSA is present in the airspace of most patients with respiratory MRSA infection or colonization, at least within 2-3 meters of the head of the patient. Whether this necessitates droplet or airborne precautions is debatable, but at the least use of regular paper masks seem warranted, especially in patients with cough or those requiring aerosolizing procedures, such as suctioning and respiratory therapy.

MRSA in HIV

Source: Shet A, et al. Colonization and subsequent skin and soft tissue infection due to methicillin-resistant *Staphylococcus aureus* in a cohort of otherwise healthy adults infected with HIV Type 1. *J Infect Dis*. 2009; 200:88-93.

MRSA COLONIZATION APPEARS TO be more common in persons with HIV infection, although there is controversy whether this is due to behavioral and environmental factors or host immunity. Nasal and axillary colonization with MRSA was prospectively assessed in a group of 107 HIV-infected patients in New York City, and compared with 52 epidemiologically matched non-HIV-infected control subjects.

Over a period of one year, MRSA colonization was observed more frequently in persons with HIV than in those without (16.8% vs. 5.8%, $p = .04$). Twenty-one MRSA isolates were recovered from 18 individuals with HIV infection, 19 of which appeared to be clonally related, as determined by the presence of the *spa* Type 1 gene. Fifteen of these isolates were characterized as MRSA300 based on the presence of PVL, SCCmec type IVa, spa type 1, and ACME (arginine catabolic mobile element) genes. In contrast, the MSSA strains recovered were heterogeneous.

Susceptibility studies showed that nearly half of the MRSA isolates found in persons with HIV infection had either constitutive or inducible resistance to clindamycin. And, 38% showed high level resistance to mupirocin.

Ten (47.8%) of the HIV+ patients with MRSA colonization subsequently developed MRSA skin and soft tissue infection. Interestingly, this was a group of fairly health HIV+ patients (mean CD4 count, 612 cell/mm^3, range 253-1401). The only significant risk factor identified for MRSA colonization in persons with HIV was a history of antibiotic use within the previous six months. The presence of a chronic skin condition, use of recreational drugs, and shared towels were not significant risk factors.

The Red Soils of Jordan: Fact or Wives Tale?

Source: Falkinham JO III, et al. Proliferation of antibiotic-producing bacteria and concomitant antibiotic production as the basis for the antibiotic activity of Jordan's red soils. *Applied Environ Microbiol*. 2009,75: 2735-2741.

SCIENTISTS CONTINUE TO SEARCH for new sources of antimicrobials. Some soils have an abiotic effect, meaning they adversely affect microbes because of their mineral content or composition. Other natural products may have a biotic, or microbial, basis for their healing properties. Intrigued by historical accounts and anecdotal reports of the beneficial healing properties of red soils found in the northwestern corner of Jordan, near the Mediterranean, Falkinham et al decided to investigate.

Jordan's red soils have been used, and continue to be used, in some parts, for treating skin infections and diaper rash. Typically, a clean area of soil is selected (without foot traffic), the superficial layer swept away, and the deeper soil collected, dried, and turned into powder or paste. This is, then, directly applied to the affected skin area.

Red soil specimens from two geographically distinct areas were collected for study. Experiments demonstrated progressive killing of both *Staphylococcus aureus* and *Micrococcus luteus* 12 and 22 days after inoculation into prepared soil specimens. No killing occurred when these same bacteria were inoculated into non-red agricultural soil specimens. Since autoclaved red soil had no killing effect on *S. aureus* or *M. luteus* strains inoculated into samples, Falkinham et al focused on a biotic effect.

Following inoculation of either *S. aureus* or *M. luteus* into soil samples, an increase in colony growth-creating zones of inhibition around *S. aureus* and *M. luteus* was observed (ranging from a 3.5- to 13-fold zone of inhibition). No increase in bacterial growth was observed in uninoculated soil samples. Similar results were observed against *C. albicans*. This bacterial growth was due to a complex of organisms, mostly consisting of Actinomycetes, various Lysobacter strains (many of which were slimy colonies with different pigmentation), and a bacillus species.

Although no baseline antibacterial activity was observed for any of the soil samples, methanol extracts of soil inoculated with either *S. aureus* or *M. luteus* showed antibacterial activity following three weeks of incubation. In contrast, by three weeks, boiled cell-free filtrates of similarly inoculated soil specimens demonstrated no activity. This suggested a specific compound, and not an enzyme, was being produced in response to inoculation with staph bacteria. Using HPLC, two compounds were subsequently identified, belonging to the actinomycin structural class of drugs, which were named Actinomycin C2 and Actinomycin C3.

Falkinham et al propose that the use of Jordan's red soil plasters, when applied directly to infected skin, stimulate the growth of antibiotic-producing microbes present in the soil, in effect providing topical antibacterial activity against common skin organisms, such as staphylococcus. ■

PHARMACOLOGY WATCH

Supplement to *Clinical Cardiology Alert*, *Clinical Oncology Alert*, *Critical Care Alert*, *Infectious Disease Alert*, *Internal Medicine Alert*, *Neurology Alert*, *OB/GYN Clinical Alert*, *Primary Care Reports*, *Travel Medicine Advisor*.

Meta-analysis Compares Antihypertensive Classes

In this issue: Comparing blood pressure medications, determining optimal length of androgen-deprivation therapy, red yeast rice for LDL reduction, and FDA Actions.

Comparison of antihypertensive classes

All classes of antihypertensive drugs are equivalent in preventing CHD and stroke according to a British study. In the largest meta-analysis of randomized trials of blood pressure reduction to date, researchers reviewed the efficacy of the 5 major classes of blood pressure medications (thiazides, beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, and calcium-channel blockers). Beta-blockers were found to have a special effect over and above that of blood pressure reduction in preventing recurrent CHD events in people with a history of CHD (29% risk reduction vs 15% with other drugs), although this affect was limited to a few years after myocardial infarction. Otherwise, the 5 main classes and blood pressure-lowering drugs were similarly effective in preventing CHD events and strokes, with the exception of calcium-channel blockers, which have a slightly higher benefit in preventing stroke (relative risk, 0.92; 95% confidence interval, 0.85-0.98). There was benefit in reducing risk of CHD and stroke with BP-lowering treatment regardless of the patient's pretreatment blood pressure, surprisingly even as low as 110 mmHg systolic and 70 mmHg diastolic. Treatment with blood pressure-lowering medications was also associated with a 13% reduction in all-cause mortality, although there was no reduction in cancer or nonvascular related deaths. The authors conclude that blood pressure lowering is important in everyone over a certain age regardless of pretreatment blood pressure and that all classes of blood pressure medications had similar effective in reducing CHD events and stroke (*BMJ* 2009;338:b1665).

Length of androgen-deprivation therapy

Men with locally invasive prostate cancer who have received external beam radiation do better with 3 years of androgen-deprivation therapy compared to 6 months of therapy according to a new study from Europe. After receiving radiation therapy, 970 men were randomly assigned to 6 months of androgen suppression (n = 483) vs 3 years of suppression (n = 487). After mean follow-up of 6.4 years, 132 patients in the short-term group and 90 patients in the long-term group had died. The number of deaths due to prostate cancer was 47 in the short-term group and 29 in the long-term group. The 5-year overall mortality was 19% vs 15.2% for short-term and long-term suppression, respectively, with an observed hazard ratio of 1.42 (P = 0.65 for non-inferiority). The authors conclude that the combination of radiotherapy plus 6 months of androgen suppression provides inferior survival as compared with radiation therapy plus 3 years of androgen suppression in men with locally advanced prostate

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cancer (*N Engl J Med* 2009;360:2516-2527). In an accompanying editorial, Peter Albertson, MD, points out the importance of determining the optimal length of androgen-deprivation therapy because of long-term side effects including weight gain, fatigue, hot flushes, osteoporosis, cardiac disease, and depression. With the high level of regular screening for prostate cancer, most men are diagnosed earlier with much lower grade disease than those addressed in this study, and it is unclear whether these findings can be applied to these men with clinically localized cancer. Radiation plus or minus androgen deprivation vs surgery, age of the patient at diagnosis, and staging of the tumor all are important in determining therapy (*N Engl J Med* 2009;360: 2572-2574).

Red yeast rice and LDL

Patients may be asking about red yeast rice for the treatment of hypercholesterolemia because of a recent study in the *Annals of Internal Medicine*. Patients were recruited from a cardiology practice in suburban Philadelphia who had had a history of statin-associated myalgias. Thirty-one patients were randomized to receive red yeast rice 1800 mg or placebo twice daily for 24 weeks. All patients were also enrolled in a 12-week therapeutic lifestyle program. Red yeast rice was effective in lowering LDL-cholesterol an average of 43 mg/dL from baseline at week 12 and 35 mg/dL at week 24 compared to reductions of 11 mg/dL at week 12 ($P < 0.001$) and 15 mg/dL at week 24 ($P = 0.011$) in the lifestyle-only group. Total cholesterol was also lowered in the treatment group, although there was no change in HDL-cholesterol or triglycerides. Treatment with red yeast rice was not associated with changes in liver enzymes or CPK levels and there was no difference in weight loss or pain severity scores between the two groups. The authors conclude that red yeast rice and therapeutic lifestyle change decreased LDL-cholesterol without increasing CPK or pain levels in patients with a history of statin-related myopathy (*Ann Intern Med* 2009;150:830-839).

The study is interesting because of the large number of patients who do not tolerate statins due to muscle pain and weakness. These patients frequently experience myalgias without myositis (normal CPK levels), and the majority continue to have symptoms despite dose adjustments or changing to a different statin. Red yeast rice is a Chinese supplement known to contain naturally occurring lovastatin (monocolin K) and other monocolins that inhibit HMG-CoA reductase, the same enzyme targeted by statins. It is unclear why red yeast rice is better tolerated than commercial statins, but the authors suggest it may be due to the relatively low dose of the statin, or other, yet undiscovered properties of red yeast rice. The authors also point out that since red yeast rice is a supplement, the chemical composition of different manufacturers is problematic and that patients should be monitored while taking the product. These findings beg the question whether low-dose generic lovastatin may be equally well tolerated, but future studies may help determine if red yeast rice has unique properties that make it an option for the many patients who do not tolerate statins and need to lower cholesterol. In 2007, the FDA issued a warning to consumers to avoid red yeast rice because it contains a pharmaceutical drug, though most products marketed in this country contain negligible amounts of lovastatin.

FDA Actions

The FDA has alerted consumers that 3 Zicam® products may result in long-lasting or permanent loss of smell (anosmia). Zicam Cold Remedy Nasal Gel, Zicam Cold Remedy Nasal Swabs, and Zicam Cold Remedy Swabs Kids Sized are all implicated, and the FDA is recommending that consumers stop using the products and throw them away. All 3 of these products contain zinc, which has not been shown to be effective in reducing the duration or severity of cold symptoms. Other Zicam oral tablets and lozenges have not been included in this advisory. Matrixx Initiatives, the manufacturer of Zicam, is offering refunds for the 3 products noted above. The company is also withdrawing the two adult products from the market — Cold Remedy Swabs Kids Sized had been previously withdrawn. There have been more than 130 reports of anosmia associated with intranasal Zicam product use ranging from 1 dose to long-term use.

The FDA has approved the first formulation of parenteral ibuprofen to treat fever and pain in hospitalized patients. The drug is given intravenously over 30 minutes in doses of 400-800 mg every 6 hours as needed for pain; lower doses are indicated for fever. As with all NSAIDs, caution is warranted when using injectable ibuprofen in patients with heart failure, renal dysfunction, increased risk for thrombosis, or history of ulcers or GI bleeding. Injectable ibuprofen is marketed by Cumberland Pharmaceuticals as Caldolor™. ■